REMARKS

OVERVIEW

Applicants have reviewed and considered the Final Office Action dated August 11, 2004 and the references cited therewith. Claims 15 and 26 have been amended. Claims 13, 14, 24, 25, 32-47 are cancelled. As a result, claims 1-16, 13-20, 24-42 are pending in this application. Applicants respectfully request reconsideration of the above identified application in view of the amendments above and remarks that follow. The changes and remarks place the claims in allowable form and in the alternative in better from for appeal.

CLAIM REJECTIONS - 35 U.S.C. § 112

Claims 43-47 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants have canceled claims 43-47 rendering this rejection moot.

CLAIM REJECTIONS - 35 U.S.C. § 103

Claims 1-6 and 15-20 and 43-47 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Tanner et al. (US Paten 5,714,377) in view of Strahl-Bolsinger et al. (Biochemi. Biophys. Acta 1426:297-307, 1999).

The Examiner states it would have been obvious to one of ordinary skill in the art to substitute for the yeast cell having a mutation in the PMT 1 gene in the method taught by Tanner et al., with a yeast cell having a mutation in the PMT 2 or a mutation in both PMT 1 and PMT 2 genes taught by Strahl-Bolsinger et al. All claims ato PMT 1 and PMT 2 have been canceled.

Applicants respectfully traverse this rejection. Applicant submitted in the last amendment evidence which the Examiner has not specifically addressed which demonstrated that PMT 2 acts surprisingly better at combatting protein misfolding than PMT 1. Claim 1 specifically recites protein folding, and the Tanner reference does not mention any correlation between protein misfolding and glycosylation, which is the crux of applicant's invention.

Further Applicants would like to point to several passages in the Stahls-Bolsinger reference which do not support the contention that PMT 2 is a clear substitution for PMT1. In fact the Stahls-Bolsinger reference teaches away from applicants' claimed invention; there is no suggestion to combine the cited references as one looking to resolve the issue of protein misfolding would not seek Tanner which speaks only to O-glycosylation, a suggestion to combine must come from the prior art and not from Applicants' specification which is the first to recognixe the interaction between protein misfolding and O-glycosylation or impermissible hindsight; the claimed invention has not been considered as a whole in that the invention involves the correction of protein misfolding, as presented in the claims in the last amendment.

The Examiner states that "it would have been obvious to one of ordinary skill in the art to substitute for the yeast cell having a mutation in the PMT 1 gene in the method taught by Tanner et al., with a yeast cell having a mutation in the PMT 2." Office Action, at page 5, first paragraph. The Examiner states that "the difference between Tanner et al. and the claimed invention is that the PMT gene is PMT 2." Office Action, at page 4, second paragraph. Not only is the there no mention in Tanner about protein misfolding, applicants respectfully further submit that Examiner is over-simplifying the relationship among the genes and cognate proteins belonging to the PMT family. To date, Strahl-Bolsinger indicates seven potential members for the PMT family sharing 50-80% homology, Strahl-Bolsinger, at page 298, col. 2, third paragraph.

PMT 2 protein shows a mere 31% identity to Pmt1. Strahl-Bolsinger, at page 298, col. 2, 2nd paragraph. Additionally, PMT proteins form differing enzyme complexes. While "Pmt1p and Pmt2 form an active enzyme complex," Strahl-Bolsinger, at page 301, col. 2, third paragraph, "[p]mt1 and pmt2 themselves form complexes with other partners." Strahl-Bolsinger, at page 302, col. 1, bridging paragraph. Strahl-Bolsinger further states that "[i]ndications have been obtained for complex formation between Pmt1p/Pmt3p and Pmt2p/Pmt6p and for Pmt4p/Pmt6p." Strahl-Bolsinger, at page 302, col. 1, bridging paragraph. Therefore, the references do not support a conclusion that pmt 2 is an obvious substitute for pmt1 since the shared homology is a mere 31% and Pmt2 forms partners with different PMT family members than Pmt1.

Therefore, claim 1 "[t]he method of producing a heterologous protein in fungi comprising: providing a recipient fungi cell wherein the expression of PMT 2 is inhibited in said cell so that incompletely folded heterologous proteins are not degraded in the endoplasmic reticulum and wherein said inhibition enhances folding and assembly of said heterologous proteins; and introducing to said recipient fungi cell a polynucleotide expression construct" is not obvious. What is more there is no mention in Tanner of the concept of any connection between protein folding and 0-glysoylation. Claims 2-6, dependent on claim 1, are likewise nonobvious as dependent on claim 1 for the reasons argued above, plus the elements in the claims.

Independent claim 15 recites "A method of producing a heterologous protein in a fungi cell comprising: providing a recipient fungi cell that has been modified by inhibiting expression of PMT 2 so that misfolded heterologous proteins are not degraded and wherein said modification enhances folding and assembly of said heterologous proteins; and introducing to said recipient fungi cell a polynucleotide expression construct, said construct comprising a DNA

sequence capable of being expressed in said cell, said gene operably linked to control sequences for expression in a fungi cell wherein said recipient fungi cell." Claim 15 recites similar elements as claim 1 and is likewise nonobvious for the reasons argued above, plus the elements in the claims. Claims 16-20, dependent on claim 15, are likewise nonobvious as dependent on nonobvious claim 15 for the reasons argued above, plus the elements in the claims. Therefore, claims 1-6 and 15-20 are patentable over Tanner (U.S. Patent 5,714,377) in view of Strahl-Bolsinger et al. Applicants request that the rejection under 35 U.S.C. §103 be withdrawn and reconsidered.

Applicants respectfully submit that the Office Action did not make out a *prima facie* case of obviousness because the cited references teach away from applicants' claimed invention. The Examiner states that Strahl-Bolsinger et al. teach that O-glycosylation can be inhibited by defects in any other PMT 1-6 genes." Applicants respectfully disagree. Strahl-Bolsinger describes that "[t]he double null mutant, pmt1pmt2 ... had residual protein mannosylation activity indicating the presence of yet further mannosyltransfereases." Strahl-Bolsinger, at page 298, col. 2, second paragraph. Therefore, the references teach away from the claimed combination because even a double null mutant for pmt1pmt2 did not completely inhibit O-glycosylation activity. A person of ordinary skill, upon reading the references, would be led in a direction divergent from the path the applicants took, i.e. using pmt 2, rather than pmt 1, 3 or 4 or a combination of pmts. Therefore, claims 1-6 and 15-20 are patentable over Tanner (U.S. Patent 5,714,377) in view of Strahl-Bolsinger et al. Applicants request that the rejection under 35 U.S.C. §103 be withdrawn and reconsidered.

Applicants respectfully submit that the Office Action did not make out a *prima facie* case of obviousness because a suggestion to combine must come from the prior art and not from

Applicants' specification or impermissible hindsight. Applicants respectfully remind Examiner that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); MPEP § 2143. Furthermore, the Examiner must avoid hindsight. *In re Bond*, 910 F.2d 831, 834, 15 U.S.P.Q.2d 1566, 1568 (Fed. Cir. 1990). Therefore, claims 1-6 and 15-20 are not obvious. In light of the above, Applicants request that the rejection under 35 U.S.C. §103 be withdrawn and reconsidered.

Applicants respectfully submit that the Office Action did not make out a *prima facie* case of obviousness because the claimed invention was not considered as a whole. In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 U.S.P.Q. 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 U.S.P.Q 698 (Fed. Cir. 1983); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 U.S.P.Q 543, 551 (Fed. Cir. 1985); MPEP § 2141.02. The invention involves the problems associated with protein misfolding and hence degradation, which is nowhere in any of the prior art references. Therefore, claims 1-6 and 15-20 when considered as a whole, are not obvious. In light of the above, Applicants request that the rejection under 35 U.S.C. §103 be withdrawn and reconsidered.

CLAIM REJECTIONS - 35 U.S.C. § 112

Claims 26-31 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner states that claim 26 and by dependence claims 27-31 lacks antecedent basis for the term "said gene" in the last line, and therefore are vague and indefinite.

Applicants thank the Examiner for this suggestion and accordingly have amended claim 26 so that it now recites "A method of producing a heterologous protein in fungi comprising: providing a recipient fungi cell wherein Bypass of Sec Thirteen expression is inhibited so that misfolded heterologous proteins are not degraded; and introducing to said recipient fungi cell a polynucleotide expression construct, said construct comprising a DNA sequence capable of being expressed in said cell, said DNA sequence operably linked to control sequences for expression in a fungi cell."

Applicants have also amended claim 15 so that it now recites "A method of producing a heterologous protein in a fungi cell comprising: providing a recipient fungi cell that has been modified by inhibiting expression of PMT 2 so that misfolded heterologous proteins are not degraded and wherein said modification enhances folding and assembly of said heterologous proteins; and introducing to said recipient fungi cell a polynucleotide expression construct, said construct comprising a DNA sequence capable of being expressed in said cell, said gene operably linked to control sequences for expression in a fungi cell wherein said recipient fungi cell." In light of the above, Applicants believe that it has overcome the rejection of claims 26-31 under 35 U.S.C. § 112 and respectfully request that the rejection be withdrawn and reconsidered.

CONCLUSION

Please charge Deposit Account No. 26-0084 in the amount of $60.00 for a one month extension from November 11, 2004 to December 11, 2004. No other fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for

any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,

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